Exhibit A
Shulman
May 96

Laboratory of Molecular Bio
Wellesley Hospital
Toronto, Ont. M4Y 1J3
27/1/93

National Cancer Institute of Canada
130 Bloor. St. W., Suite 1001
Toronto, Ont. M5S 2T7

To whom it may concern:

I am pleased to write this letter in support of Gabrielle Boulianne's application for a predoctoral fellowship.

Ms. Boulianne has been a graduate student with me since 1.Dec.,1982. Since that time her major project has been to use the recombinant DNA and hybridoma technologies to generate antibodies where the variable regions of the mouse are joined to the constant regions of the human. In this way she hopes to provide a general method of making antibodies of any specificity which do not provoke an immune response in humans and are therefore suitable for therapeutic administration to patients.

Although this is only her first year as a graduate student, she has an excellent command of both the practical and theoretical background knowledge required for advanced work in eukaryote molecular biology. She works very hard and with enthusiasm, and because of her background, her work is always on target. Her progress in her research project has been outstanding.

Yours sincerely,

Dr. Marc J. Shulman

Georges Köhler and we published several papers together, including a paper (with C.D. Wilde) on the generation of Sp 2/0 (Nature 276:269 (1978)). The cell line derivative Sp 2/0 (as well as X63-Ag8.653) was publicly available prior to March 1983.

3. Shortly after moving to Toronto, I began an extensive collaboration with Dr. Nobumichi Hozumi and members of his laboratory, notably Robert Hawley and Atsuo Ochi. This work was directed to using recombinant DNA technology to study the molecular biology of Ig genes and their function. Our work included investigating the expression of cloned light and/or heavy chain Ig genes in mutant hybridomas that had lost the ability to synthesize endogenous light and/or heavy Ig chains.

4. Also while at the Basel Institute, I met and collaborated with Dr. Christof Heusser. After I left the Institute in 1979, I maintained contact with Dr. Heusser and met with him at Ciba-Geigy's Basel research laboratories in the autumn of 1982. At that time, I discussed the above-noted successful Ig expression results with Dr. Heusser and asked him what antibody type he thought would be worth making. He suggested making mouse/human chimeric Ig's (i.e., mouse variable region with a human constant region), and we planned some specific project details. It was my understanding at that time that complete Ig could be produced by the expression of Ig light and heavy chains in a single cell of an appropriate cell line. This was based in part on observations made by Dr. Ochi and myself that mutant hybridoma cell lines, which had lost their functional light and/or heavy chain genes, nevertheless maintained their production of the other cellular components necessary for Ig gene expression. These so-called "immunocompetent hosts" could therefore express Ig transgenes.

5. In about September 1982, Gabrielle Boulianne began her studies at the University of Toronto. Her work to make mouse/human chimeric antibodies commenced in about December 1982.

6. Attached as Exhibit A is a copy of a reference letter dated January 27, 1983 sent to the National Cancer Institute of Canada funding agency regarding Gabrielle Boulianne's work. Attached as Exhibit B is a copy of a research proposal dated February 1983, prepared by Gabrielle Boulianne and myself. This proposal described the desirability of chimeric antibodies that could be non-immunogenic in humans. The proposal described a strategy for constructing chimeric genes encoding immunoglobulin heavy and light chains, each having a mouse variable region and constant region. As noted, a method for expressing both genes in the same cell had been developed by Drs. Ochi and Hozumi and communicated to me. Attached as Exhibit C is a copy of a report dated September 1983, which was sent to the Arthritis Society, an agency providing funding for my laboratory. Among other things, this report summarized Gabrielle Boulianne's chimeric antibody work in my laboratory. As indicated therein, at least by September 1983, antibody with a chimeric heavy chain had been produced and determined to retain antigen binding capacity. Attached as Exhibit D is a copy of an abstract, entitled "The Production of Chimeric Mouse/Human Antibodies", published in conjunction with the "Cellular and Molecular Biology of Neoplasia" international symposium held from October 2-6, 1983 at Honey Harbor, Ontario, Canada.

7. In an earlier declaration dated 21st May 1994, I described a presentation I made in March 1983 to the Clinical Ligand Assay Society. In fact, I had decided to present at that time, in a public, scientific forum, the concept of chimeric antibodies and how to produce them by transfecting chimeric Ig genes into immunocompetent cell lines. Because this represented a significant event to me, I have kept copies of various documents related to this presentation. On May 21, 1994, I signed that declaration in the United States under penalty of perjury and I stand by it today. (A copy of this declaration is attached). MS

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and

the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

15 May 1996
Date

Marc J. Shulman

h:\home\wms\bristol\shulman.dc2